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(21) International Application Number: PCT/US93/08983 (22) International Filing Date: 22 September 1993 (22.09.93) (30) Priority data: 07/950,380 22 September 1992 (22.09.92) US (71) Applicant: THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Office of Technology Transfer, National Institute of Health, Box OTT, Bethesda, MD 20892 (US). (72) Inventors: WILSON, Wyndham, H. ; 6010 34th Place, NW, Washington, DC 20015 (US). WITTES, Robert ; 2324 California Street, NW, Washington, DC 20008 (US).		(74) Agents: FEILER, William, S. et al.; Morgan & Finnegan, 345 Park Avenue, New York, NY 10154 (US). (81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: USE OF TAXOL FOR TREATING LYMPHOMAS AND BREAST CANCER (57) Abstract <p>The present invention is a method of treatment for a patient with cancer. In particular, it is a method of treating patients having lymphomas or breast cancer using the microtubule agent, Taxol. The present method of administration serves to prevent or retard the adverse side effects associated with Taxol and reduces the chances of a patient developing mdr Taxol resistance. The novel method of treatment provides a low-dose, long term exposure to Taxol in a patient.</p>		

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USE OF TAXOL FOR TREATING LYMPHOMAS AND BREAST CANCER

Field of the Invention

5 The present invention relates to a method of treating patients that have lymphoma or breast cancer.

More particularly, the invention relates to treatment of patients with a taxol solution administered as a 96 hour continuous infusion every 21 days.

Background of the Invention

10 Taxol is a microtubule agent isolated from the stem bark of Taxus brevifolia, the western (Pacific) yew tree. Taxol acts by promoting the formation of unusually
15 stable microtubules, inhibiting the normal dynamic reorganization of the microtubule network required for mitosis and cell proliferation (Schiff, P.B., et al. (1979) Nature 277, 665; Schiff, P.B., et al. (1981) Biochemistry 20, 3247). In the presence of Taxol, the
20 concentration of tubulin required for polymerization is significantly lowered; microtubule assembly occurs without GTP and at low temperatures, and the microtubules formed are more stable to depolymerization by dilution, calcium, cold, and inhibitory drugs. Taxol will reversibly bind to
25 polymerized tubulin, and other tubulin-binding drugs will still bind to tubulin even in the presence of Taxol.

30 Taxol interacts with the microtubule system of many types of organisms. For example, in mammalian cells a 50 Nm Taxol concentration usually causes a significant increase in microtubule number, with changes in cell shape and mitotic arrest in actively dividing cells. (Parness, J., et al. (1982) Biochem. Biophys. Res. Commun. 105, 1082). These perturbations of microtubule function caused by Taxol have a critical impact on the cell because of the

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- role played by microtubules in cell motility, secretion, and cell division.

Taxol has been studied for its effect in combating tumor growth in several clinical trials using a variety of administration schedules. Severe allergic reactions have been observed following administration of Taxol. However, it has been demonstrated that the incidence and severity of allergic reactions is affected by the rate of Taxol infusion (Weiss, R.B., et al. (1990) J. Clin. Oncol. 8, 1263).

Cardiac arrhythmias are associated with Taxol administration, and like allergic reactions, their incidence is affected by the rate of Taxol administration. Sinus bradycardia and Mobitz II arrhythmia will develop in approximately 40% and 5% of patients, respectively, beginning 4-6 hours after the start of a Taxol infusion, and continuing for 4-8 hours after its completion. In most patients, the abnormal rhythm is hemodynamically stable and does not require cardiac medications. Additionally, it has been observed that the incidence of severe cardiac events is low in patients receiving Taxol alone. Thus, infusion times up to 24 hours have been used in treatment with Taxol to decrease the incidence of toxicity and allergic reaction to the drug. Data from these studies indicates that reversible myelosuppression is the dose limiting toxicity, with significant peripheral neuropathy observed at doses of 275 mg/M² and greater. Other toxicities include myalgia, mucositis, and alopecia.

Clinical studies of Taxol have been performed in a number of tumors including acute leukemias, breast cancer, ovarian cancer and melanoma. In one study of 34 patients with ovarian cancer treated with 250 mg/M² Taxol as a 24 hour continuous infusion, there was a 21% objective response rate (Enzig, A.I. (1990) Proc. AACR 31, 187). The major toxicities were neutropenia and peripheral neuropathy. Another study of 30 patients with

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- o melanoma treated with the same dose and schedule of Taxol exhibited an objective response rate of 13% (Enzig, A.I. (1988) Proc. ASCO 7, 249).

Rowinsky, E.K., et al. ((1989) Cancer Res. 49, 4640) describes a phase I study of Taxol in 17 patients with refractory acute leukemia. Taxol was administered as a 24 hour continuous infusion and escalated from 200 to 390 mg/M². Severe mucositis limited further dose escalation, and other nonhematological effects included peripheral neuropathy, alopecia, myalgias, arthralgias, nausea, vomiting, and diarrhea. Based on this study, the maximum tolerated dose and recommended phase II doses for Taxol were 390 and 315 mg/M², respectively. Nine patients had transient reductions in peripheral blood and bone marrow blasts, and three patients had complete clearance of leukemia for less than one month.

Two mechanisms of Taxol resistance have been identified in vitro. In one type of cell, resistance is on the basis of drug efflux, and like other multidrug-resistant (mdr) cell lines, it has increased levels of membrane P-glycoproteins(s), and shows increased drug efflux (Gupta, R.S. (1985) Cancer Treat. Rep. 69, 515). These cells are also resistant to the vinca alkaloids, doxorubicin, and other natural products, and resistance is reversible with calcium channel blockers such as verapamil (Racker, E., et al. (1986) Cancer Treat. Rep. 70, 275). Another mechanism of resistance found in other taxol-resistant cells involves mutations in the alpha- or beta-tubulin subunits, with some of these cell lines actually requiring taxol for growth and mitotic spindle formation (Schibler, M.J., et al. (1986) J. Cell Biol. 102, 1522).

A potentially important factor in the area of Taxol research involves the multidrug resistant gene (mdr). The product of this gene, called the p170 glycoprotein, has been demonstrated in vitro to play a role in resistance of tumor cells to Taxol. It has been

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o demonstrated that p170 functions as a membrane pump which actively transports intracellular drug out of the cell. Using in vitro cell models, several classes of drugs have been identified which block the action of p170, including cyclosporin A, calcium channel blockers, phenothiazines, and anti-arrhythmic drugs such as quinidine and amiodarone. These drugs have been shown to reverse mdr-induced drug resistance by increasing intracellular drug concentrations.

Investigators have found increased expression of mdr in a variety of tumor types, including lymphoma and breast cancer. For example, Goldstein, L.J., et al. ((1989) J. Nat'l Com. Inst. 81, 116) reports moderately increased mdr expression in 22% (4/18) of untreated lymphomas and in 60% (3/5) of treated lymphomas. Although it is unknown if increased mdr expression is a clinically relevant mechanism of drug resistance, there is in vitro evidence that mdr plays a role in drug resistance to Taxol.

Although it is clinically unknown whether Taxol, an antimicrotubule agent effective in the treatment of cancer, is less effective in cells expressing the mdr gene, in vitro data shows that this is a concern. Furthermore, no one has been able to demonstrate an effective regimen for treatment of lymphomas and breast cancer which overcomes the problem of mdr drug resistance. The present invention discloses a method of treating lymphomas and breast cancer with a low-dose long term exposure to Taxol. There is clinical and laboratory evidence that long infusion times, on the order of 72-96 hours, may enhance the activity of drugs, such as Taxol, which are transported by P-glycoprotein. (Lai, G.M., et al. (1991) Int. J. Cancer, 49, 696). Thus the method of the present invention is to administer taxol as a 96 hour infusion in patients with lymphomas or breast cancer, to

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- effectively treat the disease and potentially reduce the chances of developing mdr Taxol resistance.

Accordingly, an object of this invention is to provide a method of Taxol treatment effective against lymphomas and breast cancer.

- 5 An additional object of this invention is to provide a method of Taxol treatment which reduces or eliminates the development of mdr Taxol resistance.

SUMMARY OF INVENTION

- 10 In accordance with these and other objects of the present invention, a method of treating lymphoma and breast cancer with Taxol, with a reduced chance of developing mdr Taxol resistance, is provided which
- 15 comprises administration of Taxol as a 96 hour continuous infusion with a dose level of between 70 and 140 mg/M²/96 hours, the dose level being dependent on the toxicity of Taxol on the patient.

- 20 This method provides an effective way of treating lymphomas and breast cancer with Taxol. Additionally, because of the low-dose prolonged exposure regimen, the chance of a patient developing mdr Taxol resistance and other adverse reactions is potentially reduced.

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DETAILED DESCRIPTION OF THE INVENTION

- For the practice of one embodiment of the present invention one must first prepare the Taxol
- 30 solution. Taxol is supplied through CTEP, DCT, NCI (IND#22850) as a concentrated solution, 6 mg/ml, in 5 ml vials (30 mg/vial) in a polyoxyethylated castor oil (Cremophor EL®) 50% and dehydrated alcohol, USP (50%) vehicle. The intact vials should be stored under
- refrigeration and diluted prior to use. When diluted in

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either 5% Dextrose Injection or 0.9% Sodium Chloride, Taxol concentrations of 0.3-1.2 mg/ml are physically and chemically stable for at least 12 hours at room temperature. (NCI Investigational Drugs; Pharmaceutical Data (1990)). It has also been demonstrated that Taxol concentrations of 0.6 mg/ml diluted in either D5W or NS and 1.2 mg/ml diluted in NS prepared in polyolefin containers are stable for at least 25 hours at ambient temperatures (20-23°C). (Waugh, et al. (1990) Am. J. Hosp. Pharm. 48, 1520).

All solutions of Taxol exhibit a slight haziness directly proportional to the concentrations of drug and time elapsed after preparation. Formulation of a small number of fibers in the solution (within acceptable limits established by the USP Particulate Matter Test for LVP's) has been observed after preparation of Taxol infusion solutions. While particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used. Therefore, in-line filtration may be necessary and can be accomplished by incorporating a hydrophilic, microporous filter with a pore size no greater than 0.22 microns (IVEX-HP In Line Filter Set-SL, 15", Abbott model # 4525 or equivalent) into the fluid pathway distal to the infusion pump.

Taxol must be prepared in non plasticized solution containers (e.g., glass, polyolefin, or polypropylene) due to leaching of diethylhexylphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing. Taxol must not be administered through PVC intravenous sets. Therefore, polyolefin- or polyethylene-line sets, such as IV nitroglycerin sets (or equivalent) should be used to connect the bottle or bag (containing the Taxol infusion solution) to the IV pump, a 0.22 micron filter is then attached to the IV set, and then may be directly attached to the patient's central

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- access device. If necessary, a polyolefin-line extension set (Polyfin™ Extension Set, MiniMed Technologies, Model # 126) can be used to provide additional distance between the IV pump and the patient's central access device.

To practice the invention, the final infusion
5 solution may be prepared by diluting the total daily Taxol dose (i.e., a 24 hour supply) in 250 or 500 ml of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP in either a glass, polyolefin or polypropylene container. Each bottle will be infused over 24 hours via
10 an infusion control device. A total of four (4) bags/bottles are required for each 96 hour infusion. Each bottle should be prepared immediately prior to use such that no more than 25 hours will elapse from the time of preparation until the end of the infusion for each
15 bag/bottle. As described above, a polyolefin- or polyethylene-line set should be used to connect the bag/bottle to the IV pump, followed by the in-line filter which will be directly attached to the patient's central access device.

20 The method of an embodiment of the present invention involves administration of Taxol infusion solution as a 96 hour continuous intravenous infusion. The Taxol solution is delivered through a permanent central intravenous catheter, with cycles repeated every
25 21 days. Therefore, before starting the therapy, patients must have a permanent or temporary central venous access.

Because of the possibility of anaphylactoid reactions, a physician should be readily available during the first 30 minutes of each infusion, and IV epinephrine,
30 hydrocortisone, and diphenhydramine should also be kept available. However, because of the prolonged 96 hour infusion, a very low incidence of reactions is anticipated.

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- o The following example illustrates a preferred embodiment of the present invention, but should not be used to limit its scope.

Example

- 5 The following criteria are used to measure the response to Taxol treatment using an embodiment of the present invention:

- Partial Remission (PR): Greater than 50% decrease in the sum of the products of the diameters of all measurable lesions for at least one month.

Minor Remission (MR): 25 to 50% decrease in the sum of the products of the diameters of all measurable lesions for at least one month.

- 15 Progressive Disease (PD): 25% or greater progression in the sum of the products of the diameter of any measurable lesion over one cycle of chemotherapy or the appearance or any new lesion consistent with metastatic disease.

- 20 Taxol was obtained as a concentrated solution, 6 mg/ml, in 5 ml vials (30 mg/vial) in 50% polyoxyethylated castor oil and 50% dehydrated alcohol. The Taxol was then diluted in 500 ml 5% Dextrose, to a concentration sufficient to supply between 17.5 and 35 mg of Taxol per square meter (based on the body surface area of the patient) over a 24 hour period. The Taxol infusion preparation was prepared between 30 and 60 minutes prior to beginning each 24 hour infusion. The Taxol infusion solution was prepared in a polypropylene lined semi-rigid container, in a volume of 500 ml.

- 30 The container [bag] with the Taxol infusion solution was connected to an IV pump via a polyethylene tube. An IVEX-HP In Line Filter Set-SL, 15", Abbott model #4525 with a pore size of 0.22 microns was then attached to the IV pump via a polyethylene line-tubing. The in-

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- o line filter was then connected to the subjects central access device.

The Taxol solution was infused over a 24 hour period, controlled by the IV pump. The procedure was repeated three more times, for a total 96 hour continuous infusion. The final dose was between 70 and 140 mg/M²/96 hours.

Twenty-three patients (11 breast, 2 Hodgkin's disease (HD), 4 mycosis fungoides (MF) and 6 non-Hodgkin's lymphoma (NHL)) were treated with the Taxol solution at the above-described rate of between 70 and 140 mg/M²/96 hrs. This 96 hr continuous infusion was repeated every 21 days, while patients were monitored for a response after every two cycles. If a patient exhibited a toxic or allergic reaction to a dose of Taxol, the dosage was lowered until tolerated. The cycles were continued until a patient exhibited disease progression or was stable for 4-6 cycles. All breast cancer patients had received a doxorubicin or mitoxantrone containing regimen for metastatic disease. Seven of these patients failed to respond, while the other four responded but did not achieve complete remission. All of the lymphoma patients failed to respond to multiple regimens within 6 months of receiving Taxol.

After treatment of the patients with the above-described Taxol infusion solution at a rate of between 70 and 140 mg/M²/96 hrs, every 21 days, patients were observed for response after every two cycles. In the breast cancer group, 9 out of the 11 patients exhibited a positive response (7 PR, 2 MR) to the treatment, for a 82% total response rate. The seven of eleven (64%) partial remission rate achieved in breast cancer patients is highly favorable over the 33% response rate reported for a 24 hour infusion at 250 mg/M² in a similar patient group. (Holmes, F.A., et al. (1991) Int'l Nat'l Cancer Inst. 83, 1797).

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o Among the lymphoma patients treated, Taxol was active in 4 out of 6 patients (3 PR, 1 MR) with diffuse large cell lymphoma. No prior treatment of lymphoma with Taxol has been reported. The 50% partial remission rate is favorable compared to the response rates determined for Taxol treatment of other cancer types.

5 The invention has been described in detail with particular reference to a preferred embodiment thereof, but it will be understood that the invention is capable of other and different embodiments. As is readily apparent to those skilled in the art, variations and modifications can be affected within the spirit and scope of the invention. Accordingly, the foregoing disclosure and description are for illustrative purposes only, and do not in any way limit the invention, which is defined only by the claims.

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o We claim:

1. Use of taxol for the manufacture of a medicament for use in a method of treating a patient suffering from lymphoma or breast cancer.

5 2. Use of a taxol infusion solution containing a concentration of taxol sufficient to provide between 17.5 milligrams and 35 milligrams of taxol per square meter of patient surface area in 24 hours, for the manufacture of a medicament for use in a method of
10 treating a patient suffering from lymphoma or breast cancer, comprising infusing the taxol solution into the patient over a period in excess of 24 hours.

15 3. Use of taxol for the manufacture of a medicament for use in a method of treating a patient, suffering from lymphoma or breast cancer, comprising infusing the medicament into the patient over a period in excess of 24 hours, wherein the medicament comprises a
20 taxol infusion solution containing a concentration of taxol sufficient to provide between 17.5 milligrams and 35 milligrams of taxol per square meter of patient surface area in 24 hours.

25 4. A use of claimed in claim 2 or claim 3, wherein the method comprises infusing the taxol solution into the patient over a period of at least 96 hours.

5. A use as claimed in any of the preceding claims, wherein the patient is suffering from a lymphoma.

30 6. A use as claimed in any of claims 1-4, wherein the patient is suffering from breast cancer.

7. A method of treating a patient suffering from lymphoma or breast cancer comprising the steps of:

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- o providing a taxol infusion solution containing a concentration of taxol sufficient to provide between 17.5 milligrams and 35 milligrams of taxol per square meter of patient surface area per 24 hours, and
infusing said solution into said patient
5 over a period of time in excess of 24 hours sufficient to cause remission of said lymphoma or breast cancer.

8. The method of claim 7, wherein said
infusing step occurs over a period of time of at least 96
10 hours.

9. The method of claims 7 or 8, wherein said
cancer comprises a lymphoma.

10. The method of claims 7 or 8, wherein said
15 cancer comprises a breast cancer.

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INTERNATIONAL SEARCH REPORT

Internat' Application No
PCT/US 93/08983

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/335

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	SECOND NATIONAL CANCER INSTITUTE WORKSHOP ON TAXOL AND TAXUS. SEPTEMBER 23-4, 1992, ALEXANDRIA, VA, NATIONAL CANCER INSTITUTE 1992 see the whole document --- -/--	1-10

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

21. December 1993

Date of mailing of the international search report

04. 01. 95

Name and mailing address of the ISA

Authorized officer

INTERNATIONAL SEARCH REPORT

Internat Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	J.NATL.CANCER INST. vol. 83, no. 24 , 1991 pages 1797 - 1805 'Phase II Trial of Taxol, an Active Drug in the Treatment of Metastatic Breast Cancer' cited in the application see page 1797 - page 1798 see page 1802; table 5 see page 1804, right column, line 15 - line 19 see page 1805, left column, line 49 - line 52 ---	1-10
Y	DIALOG INFORMATION SERVICES, FILE 159, CANCERLIT, ACCESSION NUMBER 00845439	1-10
Y	& THIRD INTERNATIONAL CONGRESS ON NEO-ADJUVANT CHEMOTHERAPY. FEBRUARY 6-9 1991, PARIS, FRANCE 1991 page 61 'Drug resistance considerations in neoadjuvant chemotherapy (meeting abstract)' see the whole document ---	1-10
Y	INT.J.CANCER vol. 49 , 1991 page 696 'P-Glycoprotein expression and schedule dependence of adriamycin cytotoxicity in human colon carcinoma cell lines' cited in the application see page 701, left column, line 1 - line 6 see page 701, right column, line 30 - line 31 see page 702, right column, line 3 - page 703, right column, line 11 -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7-10 are directed to a method of treatment of
(diagnostic method practised on) the human/animal body the search has been
carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.